Interference No. 105,358
Filed on behalf of Junior Party REDDY
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Paper No. ___

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES
(Administrative Patent Judge Michael P. Tierney)

POLICE S. **REDDY**, SURESH K. TIKOO, and
LORNE A. BABIUK,
(U.S. Patent 6,492,343)
Junior Party,

v.

MICHAEL A. **JOHNSON**, JEFFREY M. HAMMOND,
RICHARD J. McCOY and MICHAEL G. SHEPPARD
(U.S. Application 09/485,512)
Senior Party,

Patent Interference No. **105,358**
(Technology Center 1600)

REDDY SUBSTANTIVE MOTION 2

(Motion under 37 CFR § 41.121(a)(I)(iii) for judgment based on unpatentability of all involved Johnson claims for failure to comply with 35 U.S.C. § 112, paragraph 1)

Johnson Exhibit _____
Reddy v. Johnson
Interference 105,538

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes

REDDY SUBSTANTIVE MOTION 2

(Motion under 37 CFR § 41.121(a)(I)(iii) for judgment based on unpatentability of all involved Johnson claims for failure to comply with 35 U.S.C. § 112, paragraph 1)

I. REQUEST FOR RELIEF

Junior party REDDY, *et al.* ("Reddy") moves under 37 C.F.R. §§ 41.121(a)(I)(iii) for judgment based on the unpatentability of all involved Johnson claims for failure to comply with the written description and enablement requirements of 35 U.S.C. § 112, paragraph 1.

II. REASONS FOR RELIEF REQUESTED

A. Background

The claims at issue in the '512 application relate to insertion of foreign genes (or "heterologous DNA") into certain regions of Porcine Adenovirus 3 (PAV3). All of Johnson's claims in interference contain limitations directed to insertions of foreign ("heterologous") DNA within certain map unit ranges. Facts ¶¶ 1, 5, and 6. A genome is "mapped" by dividing the whole genome into 100 units. Fact ¶ 2.

If the foreign genes are inserted into a location that codes for polypeptides that are essential to viral replication, then the resulting adenovirus is "replication-defective." Fact ¶ 85. Replication-defective adenoviruses cannot be grown except in a complementing "helper" cell-line that can produce the essential products of the deleted region or regions of the adenovirus. Fact ¶¶ 86-87. In the absence of a complementing cell-line, viral DNA that has been recombined to eliminate or disable one or more essential genes will not express a virus. Fact ¶ 87. Such recombinants are therefore known as "helper-dependent" recombinants. Fact ¶ 88. By experimentation it is sometimes possible to identify certain areas of the adenovirus genome that are not essential to viral replication. Fact ¶ 89.

Johnson's claims in interference contain limitations directed to the incorporation of foreign DNA into PAV3 at map units 50-55, 55-65, 72-85. Fact ¶ 6. These map unit ranges are not described or mentioned anywhere in the '512 application. Fact ¶ 14-15, 21. Rather, they were submitted for the first time on August 13, 2004, shortly before *ex parte* prosecution of the application was suspended. Fact ¶ 15. Moreover, these map unit ranges correspond to areas of PAV3 that are predicted to be essential for viral replication, and insertions made in those map unit ranges are highly likely to disrupt the expression of one or more these essential areas. Fact ¶ 23-28. The '512 application does not describe or enable the helper cell lines needed to grow replication-defective virus. Fact ¶¶ 32-34.

The two map unit ranges that are disclosed in the '512 application are ranges 81-84 and 97-99.5. Fact ¶¶ 37, 56. However, as discussed below both of these regions also incorporate regions of the genome that are essential to viral replication. Fact ¶¶ 36-51, 56-69.

B. Legal Standard

All of the Johnson claims in interference are unpatentable because the '512 application fails to adequately describe and enable them in terms sufficient to fulfill the requirements of 35 U.S.C. § 112 paragraph 1. The written description requirement ensures "that, as of the filing date, the inventor conveyed with reasonable clarity to those of skill in the art that he was in possession of the subject matter" in question. *Union Oil Co. v. Atlantic Richfield Co.*, 208 F.3d 989, 997, 54 U.S.P.Q.2d 1227, 1232 (Fed. Cir. 2000). The application "itself must describe an invention, and do so in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought." *Lockwood v. American Airlines, Inc.*, 107 F.3d

1565, 1572. 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997); *see also In re Barker*, 559 F.2d 588, 592 n. 4, 194 U.S.P.Q. 470, 473 (CCPA 1977) (the essential goal of the written description requirement is "to clearly convey the information that an applicant has invented the subject matter which is claimed"). The purpose of the written description requirement "is to ensure that the scope of the right to exclude . . . does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification." *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345, 54 U.S.P.Q.2d 1915, 1917 (Fed. Cir. 2000).

To be enabling, "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed."[1] *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1374, 52 U.S.P.Q.2d 1129, 1138 (Fed. Cir. 1999). The scope of the claims must "bear a reasonable correlation to the scope of enablement provided by the specification[.]" *See In re Wright*, 999 F.2d 1557, 1561, 1562-64, 27 U.S.P.Q.2d 1510, 1513, 1514-15 (Fed. Cir. 1993) (affirming PTO's rejection of claims where the single example in the specification, which was limited to a description of the production of a recombinant vaccine that conferred immunity in chickens against a certain type of RNA tumor virus, did not enable the full scope of the claims to "*any and all* live, non-pathogenic vaccines, and processes for making such vaccines, which elicit immunoprotective activity in *any* animal toward *any* RNA virus") *id. In re Wright*, 999

[1] Whether claims are sufficiently enabled is determined as of the date the patent application was first filed, which in this case is August 1997. *Enzo BioChem, Inc.*, 188 F.3d at 1371, 54 U.S.P.Q.2d at 1135.

F.2d at 1562, 27 U.S.P.Q.2d at 1513; *In re Goodman*, 11 F.3d 1046, 1049, 29 U.S.P.Q.2d 2010, 2012-13 (Fed. Cir. 1993) (the PTO did not err by rejecting, on enablement grounds, applicant's broad claims to a method for producing any type of mammalian protein in any type of plant cell where the specification included only a single working example that was directed to only one particular species of plants).

An applicant cannot rely on what was well known in the art as a substitute for an enabling disclosure of his invention. As the Federal Circuit held:

> [R]easonable detail must be provided in order to enable members of the public to understand and carry out the invention. . . . . It is true . . . that a specification need not disclose what is well known in the art. However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement.

Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1366, 42 U.S.P.Q.2d 1001, 1005 (Fed. Cir. 1997) ("*Novo Nordisk*") (citations omitted) (invalidating patent because specification failed to enable practice of the claimed method). The Federal Circuit has explained that "it is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement." *Id.*

Where the art is unpredictable, "the required level of disclosure will be greater than, for example, the disclosure of a 'predictable' factor such as a mechanical or electrical element." *In re Vaeck*, 947 F.2d 488, 496, 20 U.S.P.Q.2d 1438, 1445 (Fed. Cir. 1991); *see also In re Goodman*, 11 F.3d at 1051. Furthermore, "[t]ossing out the mere germ of an idea does not constitute enabling disclosure." *Enzo BioChem, Inc.*, 188 F.3d at 1374, 52 U.S.P.Q.2d at 1138 (*citing Novo Nordisk.*, 108 F.3d at 1366, 42 U.S.P.Q.2d at 1005).

C. The '512 Application Does Not Describe or Enable PAV3 Incorporating Foreign DNA at Insertion Sites MU 50-55, 55-65, or 72-85.

Johnson claim 1 reads:

> A recombinant porcine adenovirus expressing heterologous DNA, said DNA of interest being stably integrated into a site of said recombinant porcine adenovirus genome wherein said site is selected from the group consisting of one or more mapping units selected from the group consisting of mapping units 50-55, 55-65, 72-85, 81-84, and 97-99.5 of PAV3.

This claim is representative of claims 1-2, 4, 26, 31, 39-40, 42, 44-65, 67, 68-69, 72-73 in that each of these claims includes within its scope recombinant adenoviruses with an insertion made in a site consisting of one or more of the map units 50-55, 55-65, 72-85.[2]

Map units 50-55, 55-65, 72-85 are not mentioned or otherwise described anywhere in the '512 specification. Fact ¶ 7. Nor were these limitations part of the original claims submitted with the '512 application. Fact ¶ 14. They were submitted for the first time on August 13, 2004, shortly before *ex parte* prosecution of the application was suspended. Fact ¶ 15. Nothing in the '512 application indicates that Johnson had conceived and reduced to practice a recombinant PAV3 incorporating foreign DNA in any of these map units. Fact ¶ 16.

During the prosecution of the '512 patent, Johnson submitted testimony identifying prior art publications where sequences allegedly corresponding to map units 50-55, 55-65, and 72-85 of PAV3 were published. Fact ¶ 17. Johnson's declaration argued that a person of skill in the art could have made insertions of foreign DNA in

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[2] Claims directed to insertions made at map units 81-84 and 97-99.5 are discussed below in sections D and E respectively.

these regions of PAV3 relying on these publications. Fact ¶ 18. Even assuming that to be true (in fact it is not true, for reasons discussed below), that still does not address the fact that these references are not cited anywhere in the '512 application. Fact ¶ 19. To fulfill the written description requirement, it is necessary for Johnson to have either disclosed the map unit limitations in the '512 application, or else to have expressly referred to or incorporated by reference the publications that disclose them. *See Forssmann v. Matsuo et al.*, 23 U.S.P.Q.2d 1548, 1551 (BPAI 1992) (description of hormone containing 126 amino acids and hormone fragments generally was insufficient to support claims to specific amino acids 99 to 126 of the hormone). Having failed to do either, the '512 application does not demonstrate that Johnson was in possession of the invention described in claims 1-4, 26, 31, 39-40, 42, 44-65, 67, 68-69, 72-73 at the time of filing. Fact ¶ 20.

Johnson first added map-unit limitations to his claims in an amendment dated February 27, 2004, in which he purported to limit his claims to the right hand end of the genome "from about 50 genomic map units to 100 genomic map units." Fact ¶ 78. He argued that support was found in the disclosure of insertions of foreign genes into the "right hand end of the genome." Fact ¶ 79. The specification makes clear, however, that the term "right hand end of the genome" in Johnson's disclosure refers only to map units 97-99.5, not the entire right half of the genome from map units 50 to 100. Fact ¶ 80. For this additional reason, the '512 application fails to describe claims directed to insertions into map units 50-55, 55-65, and 72-85 of PAV3.

The '512 application also fails to enable the above-listed claims. First, no gene sequence is provided for the these segments of PAV3, nor are the restriction enzymes

associated with these segments identified. Fact ¶ 21. Accordingly, the '512 application does not provide any teaching to enable a person of skill in the art to make insertions within these segments. Facts ¶ 22 and 27.

Second, each of regions 50-55, 55-65, and 72-85 of PAV3 includes nucleotides that are associated with genes coding for structural proteins that are predicted to be essential for viral replication. Facts ¶¶ 23 and 26. Specifically, map units 50-55, 55-65, 72-85 encompass coding regions for PAV3 pVI, pX, pV, endonuclease, hexon, pVIII, 33K and 100K. Fact ¶ 24. Reddy's PAV3 genome map shows this. Fact ¶ 25. Each of these regions contain genes that express structural elements, including pVI, hexon and the pVIII proteins, without which PAV3 has not been shown to be able to replicate except with the use of a helper cell line. Fact ¶ 26. Insertions made in these regions would likely disable these genes, thus rendering the recombinant virus replication-defective. Fact ¶ 28.[3]

Nothing in the '512 application teaches the use of helper cell lines that would make it possible for a person of ordinary skill in the art to grow a replication-defective virus. Fact ¶ 32. Nor were suitable PAV3 helper cell lines available in the art at the time the '512 application was filed. Facts ¶¶ 33 and 34. Accordingly, even if a person of skill in the art could have succeeded in making an insertion in one of the above-listed regions in PAV3 viral DNA, the resulting recombinant DNA would likely not form a virus. Facts ¶¶ 28 and 31. Accordingly, such a person would fail to create a "porcine adenovirus" of

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[3] The '512 application teaches insertion of "cassettes" of homologous DNA that include polyA signals which signal the end of transcription. Fact ¶ 29. Inserting a polyA signal into the middle of a gene disables expression of the gene. Fact ¶ 30.

the claims. Facts ¶¶ 28 – 31. Thus, the '512 application fails to enable a person of ordinary skill in the art to practice the full scope of Johnson claims 1-4, 26, 31, 39-40, 42, 44-65, 67, 68-69, 72-73. Fact ¶ 22.

D. The '512 Application Does Not Enable PAV3 Incorporating Foreign DNA at Map Units 97-99.5

Johnson claims 28 and 71 are directed to a recombinant PAV3 incorporating foreign DNA in the region identified as encompassing map units 97 to 99.5. Fact ¶ 36. Representative claim 28 reads:

> A recombinant vector as claimed in claim 2 wherein said heterologous DNA is stably integrated into the right hand end of the genome at map units from about 97 to about 99.5.

Fact ¶ 36.

The '512 application teaches that map units 97-99.5 encompass:

> . . . non-essential regions of the viral genome which may be suitable for the purposes of replacement with or insertion of heterologous DNA.

Fact ¶ 37.

No matter how the claim term "97-99.5" is construed,[4] map units 97-99.5 in fact encompass nucleotides that are indeed essential to viral replication. Fact ¶ 40. Accordingly, for the same reasons that the '512 application fails to enable the practice of the full scope of claims directed to insertions at map units 50-55, 55-65, and 72-85, so too

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[4] As explained in Reddy's Substantive Motion No. 3, the claims' reference to "map units" is hopelessly ambiguous. No matter how the map units are construed, however, the claims are not enabled.

does it fail to enable the scope of claims directed to insertions at map units 97-99.5. Fact ¶ 54.

Early region 4 ("E4") of PAV3 includes genes that are essential to viral replication. Facts ¶41 and 42. As shown in the genome maps above, map units 97-99.5 plainly encompass the E4 region. Fact ¶ 8. Accordingly, insertions made between map units 97-99.5 can be expected in some cases to disable the genes expressed in E4, thus rendering the virus replication-defective. Fact ¶ 42.

Figure 4 of the '512 application purports to identify the putative TATA site for the E4 promoter, "this being the left most end for the possible site of insertion." Fact ¶ 39. A TATA site is a sequence of nucleotides that is essential for the expression of the genes that are associated with it. ¶ 40.

The figure identifies the referenced TATA site in bold type at nucleotides 698-701. Fact ¶ 43. The map unit range of 97 to 99.5 of claim 28 approximates the area between the bolded ITR and the bolded TATA site in Figure 4. Fact ¶ 44. Presumably, Johnson identifies the E4 promoter as the "left most end" for insertion because he expects that if the E4 promoter were disabled, the resulting virus would be rendered replication-defective. Facts ¶¶ 39-42.

The TATA site called out in Figure 4, however, is in fact not the TATA site for the E4 promoter; on the contrary, it is located in the middle of E4 open reading frame 2. Fact ¶ 45. The true TATA site for the E4 promoter is located much closer to the ITR, and is shown at nucleotides 326 through 329 in Figure 4. Facts ¶ 46 and 47. This is well within map units 97 to 99.5. Fact ¶ 44. Thus, the range 97 to 99.5 is mischaracterized in the '512 Application. Facts ¶¶ 49-51. The reader of the '512 Application is led to

believe that the 97 to 99.5 range does not encompass the E4 promoter, when in fact it clearly does. Facts ¶¶ 47-51.

Following the teachings of the '512 application, a person of ordinary skill in the art attempting to practice the full scope of the claims would make some insertions that would disable the essential genes of the E4 region. Facts ¶¶ 51 and 52. As discussed above, replication-defective viruses are not enabled in the '512 application because helper cell lines capable of growing replication-defective viruses were not known in the art and are not disclosed in the application. Facts ¶¶ 32 and 33. Accordingly, based on the teachings of the '512 application and the prior at as it was at the time of filing, it would not have been possible for a person of ordinary skill in the art to practice the full scope of claims 28 and 71. Facts ¶¶ 51-54.

E. The '512 Application Does Not Enable PAV3 Incorporating Foreign DNA in the E3 Region at Map Units 81 to 84.

Johnson claim 30 is directed to:

> A recombinant vector as claimed in claim 2 wherein said heterologous DNA is stably integrated into the adenovirus E3 region of the genome at map units from about 81 to about 84.

The '512 Application fails to describe or enable the full scope of this claim.

First, the '512 application does not describe or enable integrations of foreign DNA into the "E3 region," as it is described and defined in the patent. E3 is described as overlapping L4, and Johnson suggests that insertions to E3 might be made after the polyadenylation signal of L4. Facts ¶ 57 and 58. E3 does not actually overlap with L4 in PAV3; rather it overlaps with L5. Fact ¶ 57. Johnson's '512 application characterizes map units 81-84 as a "non-coding region" of E3. Fact ¶ 56. However, there is no non-coding region in E3. Fact ¶ 57. E3 encodes for several genes that modulate the response

of the host cells to adenovirus infection. Fact ¶ 65. Thus, the '512 Application does not enable insertions into a non-coding region. Further, there is no portion of E3 after the polyadenylation signal of L5. Fact ¶ 62. E3 and L5 share a common polyadenylation signal, which indicates that they are co-terminal. Id. Accordingly, it is impossible to follow Johnson's suggestion to make an insertion into E3 after the polyadenylation of L5.

Second, the '512 application does not describe or enable integrations of foreign DNA "at map units from about 81 to 84." As explained in Reddy's Substantive Motion 3, the "about 81 to 84" limitation of this claim is indefinite because it does not specify to which nucleotides it refers and the '512 is inconsistent in its description of the size of the genome. If the Board were to construe the claim, however, it should employ the principle that claims in prosecution should be given their broadest reasonable construction. See, *In re Hyatt*, 211 F.3d 1367, 1372 (Fed. Cir. 2000); *Scripps Research Institute v. Genentech, Inc.*, 2005 Pat. App. LEXIS 19, *10 (B.P.I.A. Feb. 28, 2005) (applying the "broadest reasonable construction" to claims in patent interference). Under such a construction, the full scope of this claim would not be enabled.

There are three possible interpretations of the range of about 81 to 84, based on the three genome sizes disclosed in the '512 application (34.8 kb, 35kb and 34,094 bp). Fact ¶ 10. Using 34,094 map units, 81 to 84 corresponds to nucleotides 27,616 to 28,639. Fact ¶ 83. Using the genome size 34.8 kb, map units 81 to 84 correspond to nucleotides 28,188 to 29,232. Fact ¶ 64. And using 35 kb map units, 81 to 84 corresponds to nucleotides 28,350 to 29,400. Fact ¶ 84. Thus, the range 81 to 84 according to the disclosure of the '512 application could reasonably be interpreted to encompass an insertion into the genome at anywhere from about nucleotide 27,616 to about nucleotide 29,232, and the broadest of the three individual ranges listed above is the range 28,350 to 29,400.

Encompassed within both of these ranges of nucleotides portion of the DNA that forms part of the essential fibre gene, which has a splice acceptor site at 28910. Fact ¶¶

66-68. Thus, some insertions that might be made within this range would disable the expression of fibre. Fact ¶¶ 29, 30, 66-69. This would render the virus replication-defective and helper-dependent. Fact ¶ 66-69. The '512 Application does not enable the use of helper cells for the reproduction of helper-dependent recombinants, however. Facts ¶ 68-70. Thus, for this reason as well, the '512 Application fails to enable the full scope of claim 30. Fact ¶ 71.

F. Claims 1, 2, 4, 28, 30, 44-62, 65, 66 and 71-73 Are Invalid Because the Claims Encompass Replication Defective Recombinant PAV3 Adenoviruses that Are Not Described or Enabled

Nearly all of Johnson's involved claims (Claims 1, 2, 4, 28, 30, 44-62, 65, 66 and 71-73) are generic claims that cover insertions into regions of PAV3 regardless of whether the region is essential or non-essential. For example, Johnson Claim 2 specifies a recombinant PAV3 adenovirus with heterologous DNA inserted into one of a specified list of insertion sites. A virus within the scope of Johnson Claim 2 could be replication competent (if the heterologous DNA was inserted into a non-essential site) or replication defective (if the heterologous DNA was inserted into an essential site). The generic nature of these claims is confirmed by the doctrine of claim differentiation: the only distinction between Claim 2 and dependent Claim 26 is the additional requirement in Claim 26 (not found in Claim 2) that the heterologous DNA be inserted into a "non-essential region." Fact ¶ 72.

When claims generically cover species, some of which are not enabled or described, the claims are invalid under section 112. *In re Goodman*, 11 F.3d 1046, 1052 (Fed. Cir. 1993) (claim generically covering gene transformation of plants invalid when the patent provided no reliable gene transformation method for use with monocot plants, and the method of transforming for monocot plants was "fraught with unpredictability"); *Adang v. Fischhoff*, 286 F.3d 1346, 1350 (Fed. Cir. 2002) (disclosure of transformation

of tobacco plant did not enable transformation of entirely different species such as tomato); *Plant Genetic Sys. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1337-1338 (Fed. Cir. 2003) (claim to plant cell having heterologous DNA stably integrated into its genome was invalid because patent did not enable insertions of heterologous DNA into monocot plants, stably transformed monocot cells were difficult to produce, and the patent gave no instruction as to how).

The Johnson claims are invalid under this rule: each of these claims generically covers insertions into essential and non-essential regions. Yet the '512 application neither describes nor enables the production of recombinant adenoviruses through insertion into essential regions. The claims therfore do not meet the requirements of section 112.

G. The '512 Application Does Not Describe or Enable Insertions Into Non-Essential Regions of PAV3

Johnson claim 26 is directed to:

> A recombinant vector as claimed in claim 2 wherein said heterologous DNA is stably integrated into the non-essential regions of the porcine adenovirus genome.

Fact ¶ 72.

The '512 application fails to describe and enable this claim because it fails to provide the reader sufficient guidance as to which regions of PAV3 are non-essential and which are essential. Fact ¶ 77. At the time of filing, it was not known which regions of PAV3 would prove to be essential for viral replication. Facts ¶¶ 73 and 74. Indeed, this is a question that is still under active investigation in the art. Fact ¶ 75. Nor is it possible to predict with confidence which regions of PAV3 are non-essential based on an understanding of other PAV serotypes or non-porcine adenovirus. Fact ¶ 76. Homology between PAV3 and other PAV serotypes is not sufficient to identify essential PAV3 regions based information that may be available regarding other PAV serotypes. Fact ¶

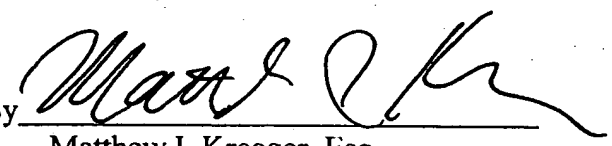
76. Certainly, homology between PAV3 and human adenovirus is not sufficient to identify the non-essential regions of PAV3 based on an understanding of the non-essential regions of human adenovirus. Fact ¶ 76. But without this information, it is impossible for a person of ordinary skill in the art to practice the full scope of this claim. Fact ¶ 77.

III. CONCLUSION

Johnson's claims fail to satisfy the written description and enablement requirements. Reddy respectfully requests that the Board grant this motion and find Johnson's claims invalid under 35 U.S.C. § 112.

Respectfully submitted,

Dated: February 24, 2006

By 

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APPENDIX A (EVIDENCE IN SUPPORT OF THE MOTION)

In support of this motion, Reddy relies on Reddy Exhibit Nos. 2001-2004, 2009, 2013, 2014, 2016, 2022, 2025, 2029, 2032, and 2033:

1. Reddy et al., U.S. Patent No. 6,492,343 (filed Apr. 14, 1999) (issued Dec. 10, 2002) (the "'343 patent") (Ex. 2001).
2. Johnson U.S. Patent Application No. 09/485,512, filed May 5, 2000 (Ex. 2002).
3. Johnson Australian Provisional Patent Application No. PO 8560, filed August 14, 1997 (Ex. 2003).
4. Johnson International Patent Application No. PCT/AU98/00648, filed August 14, 1998 (Ex. 2004).
5. Declaration of Katherine J. Spindler, Ph.D. dated February 22, 2005. (Ex. 2009).
6. Johnson Clean Copy of Claims, 9 pages (Ex. 2013).
7. Thomas Shenk, Ch. 67: *Adenoviridae: The Viruses and Their Replication.* FIELDS VIROLOGY, 2111-2148 (3rd ed., B.N. Fields et al. eds. Lippincott – Raven Publishers, Philadelphia, 1996). (Ex. 2014).
8. Marshall S. Horwitz, Ch. 68: *Adenoviruses,* FIELDS VIROLOGY B. N. Fields B.N. et al. eds. Lippincott – Raven Publishers, Philadelphia, 2149-2171 (1996) (Ex. 2016).
9. P. Seshidhar Reddy et al., Sequence Analysis of Putative pVIII, E3 and Fibre Regions of Porcine Adenovirus Type 3, VIRUS RESEARCH 36, 97-106. (1995) (Ex. 2022).

10. P. Seshidhar Reddy et al., *Characterization of the early region 4 of porcine adenovirus type 3*, VIRUS GENES 15, 87-90 (1997) (Ex. 2025).

11. P. Seshidhar Reddy et al., *Nucleotide Sequence and Transcription Map Of Porcine Adenovirus Type 3,* VIROLOGY 251(2):414-426 (1998) (Ex. 2029).

12. Response to Final Office Action filed with the U.S. Patent and Trademark Office on August 13, 2004, 9 pages (Ex. 2032).

13. Second Declaration of Dr. Jeffrey Michael Hammond Under 37 C.F.R. §1.132, 7 pages, with Response to Office Action mailed on February 27, 2004, 19 pages (Ex. 2033).

APPENDIX B (STATEMENT OF MATERIAL FACTS)

1. Claim 1 of the '512 application is directed to a PAV3 vector where the insertion site is "selected from the group consisting of one or more mapping units selected from the group consisting of mapping units 50-55, 55-65, 72-85, 81-84, and 97-99.5 of PAV3." (Ex. 2002 and Ex. 2009 Spindler Decl. at ¶¶ 36 and 54 (*citing* Ex. 2013)).

2. A genome is "mapped" by dividing the whole genome into 100 units. (Ex. 2009 Spindler Decl. at ¶ 18).

3. At the time that the '512 application was filed, the full genome of PAV3 had not been sequenced, and the arrangement of the various elements of PAV3 that had been sequenced had not been published. (Ex. 2002 and Ex. 2009 Spindler Decl. at ¶¶ 31 and 32 (*citing* Ex. 2029 at page 420, Figure 1)).

4. The specific point to which a given map unit (for example, 81) refers depends on the size of the genome. Map unit 81 refers to the 810th base in a genome of 1000 base, and to the 4,050th base in a genome of 5000 bases, for example. (Ex. 2009 Spindler Decl. at ¶ 18).

5. All of Johnson's claims contain one or more map unit limitations of the kind included in Claim 1. (Ex. 2009 Spindler Decl. at ¶ 54 (*citing* Ex. 2002)).

6. Claims 1-4, 26, 31, 39-40, 42, 44-65, 67, 68-69, and 72-73 each specify that insertion of the foreign DNA is to be made in one or more of the map unit ranges 50-55, 55-65, or 72-85. (Ex. 2009 Spindler Decl. at ¶ 55 (*citing* (Ex. 2002, at page 22-26, and preliminary amendment at pages 1 and 2)).

7. Map units 50-55, 55-65, and 72-85 are not mentioned or otherwise described anywhere in the '512 application, and the '512 application does not incorporate by reference any publications that disclosed the sequences of these regions. (Ex. 2009 Spindler Decl. at ¶ 56 (*citing* Ex. 2002)).

8. Reddy published a paper in 1998 that included a "genome map" of PAV3 that shows the arrangement of the PAV3 genes in the genome. (Ex. 2009 Spindler Decl. at ¶ 31 (*citing* Ex. 2029 at page 420, Figure 1)).

9. Johnson's Australian priority application describes the size of the PAV3 genome as being 34.8 kb. (Ex. 2003 at page 4, line 21).

10. In its present form, the '512 Application simultaneously discloses three different sizes for the PAV3 genome. These are 34.8 kb, 35kb and 34,094 bp. (Ex. 2009 Spindler Decl. at ¶ 37(*citing* Ex. 2002 at page 3, lines 27-28; Figure 1; and Figure 15)).

11. The reference to 35kb appears for the first time in the original PCT filing at Figure 1. (Ex. 2004).

12. The '512 Application nowhere defines which of these three sizes is to be used as the basis for the map unit ranges set forth in the claims. (Ex. 2009 Spindler Decl. at ¶ 37 (*citing* Ex. 2002)).

13. Reddy demonstrated in 1998 that the correct size of the PAV3 genome is 34,094 bp. (Ex. 2009 Spindler Decl. at ¶ 35 (*citing* Ex. 2029)).

14. Map units 50-55, 55-65, and 72-85 were not part of the original claims submitted with the '512 application. (Ex. 2002 and Ex. 2009 Spindler Decl. at ¶ 56).

15. The limitations of map units 50-55, 55-65, and 72-85 were submitted for the first time on August 13, 2004, shortly before *ex parte* prosecution of the application was suspended. (Ex. 2032)

16. Nothing in the '512 application indicates that Johnson had conceived and reduced to practice a recombinant PAV3 incorporating foreign DNA in any of the map units 50-55, 55-65, and 72-85. (Ex. 2009 Spindler Decl. at ¶¶ 55-60 (*citing* Ex. 2002 at page 22-26, and preliminary amendment at pages 1 and 2)).

17. During the prosecution of the '512 patent application, Johnson submitted testimony identifying prior art publications where sequences allegedly corresponding to

map units 50-55, 55-65, and 72-85 of PAV3 were published. (Ex. 2009 Spindler Decl. at ¶ 48 (*citing* Ex. 2033)).

18. Johnson's declaration argued that a person of skill in the art could have made insertions of foreign DNA in these regions of PAV3 relying on these publications. (Ex. 2033 and Ex. 2009 Spindler Decl. at ¶ 56).

19. Even assuming that to be true (in fact it is not true, for reasons discussed below), that still does not address the fact that these references are not cited anywhere in the '512 application (Ex. 2009 Spindler Decl. at ¶¶ 55-60 (*citing* Ex. 2002)).

20. Having failed either to disclose the map unit limitations in the '512 application, or to have expressly referred to or incorporated by reference the publications that disclose them, the '512 application does not demonstrate that Johnson was in possession of the invention described in claims 1-4, 26, 31, 39-40, 42, 44-65, 67, 68-69, 72-73 at the time of filing. (Ex. 2002; Ex. 2009 Spindler Decl. at ¶¶ 55-60 (*citing* Ex. 2002)).

21. No gene sequence is provided for map units 50-55, 55-65, and 72-85 of PAV3, nor are the restriction enzymes associated with these segments identified in the '512 application. (Ex. 2009 Spindler Decl. at ¶ 56 (*citing* Ex. 2002)).

22. The teachings of the '512 Application do not enable one of skill in the art how to make and use a PAV3 vector with insertions within map units 50-55, 55-65, 72-85 without undue experimentation. (Ex. 2009 Spindler Decl. at ¶ 60 (*citing* Ex. 2002)).

23. Map units 50-55, 55-65, 72-85 correspond to areas of PAV3 that are predicted to be essential for viral replication based on what was known about human adenovirus type 2. (Ex. 2009 Spindler Decl. at ¶ 57 (*citing* Ex. 2014, Shenk, at page 2131, right column)).

24. Specifically, map units 50-55, 55-65, 72-85 encompass coding regions for PAV3 pVI, pX, pV, endonuclease, hexon, pVIII, 33K and 100K. (Ex. 2009 Spindler Decl. at ¶ 57 (*citing* Ex. 2001, '343 patent at Figure 2)).

25. Reddy's PAV3 genome map shows that map units 50-55, 55-65, 72-85 encompass coding regions for PAV3 pVI, pX, pV, endonuclease, hexon, pVIII, 33K and 100K. (Ex. 2009 Spindler Decl. at ¶ 31 (*citing* Ex. 2029 at page 420, at Figure 1)).

26. None of pVI, pX, pV, endonuclease, hexon, pVIII, 33K and 100K is known to be non-essential for PAV3 replication. (Ex. 2009 Spindler Decl. at ¶ 57 (*citing* Ex. 2001)).

27. The '512 application does not teach the locations and characterizations, if any, of non-essential regions within map units 50-55, 55-65, 72-85 of PAV3. (Ex. 2009 Spindler Decl. at ¶ 57 (*citing* Ex. 2002)).

28. Insertions made in map unit regions 50-55, 55-65, 72-85 of PAV3 are highly likely to disrupt the expression of one or more of pVI, pX, pV, endonuclease, hexon, pVIII, 33K and 100K. (Ex. 2009 Spindler Decl. at ¶¶ 57-58 (*citing* Ex. 2002)).

29. The '512 application teaches insertion of "cassettes" of homologous DNA that include polyA signals which signal the end of transcription. (Ex. 2009 Spindler Decl. at ¶ 56 (*citing* Ex. 2003, at page 14, lines 4-9.)).

30. Inserting a polyA signal into the middle of a gene disables expression of the gene. (Ex. 2009 Spindler Decl. at ¶ 22).

31. Disruption of the expression of pVI, pX, pV, endonuclease, hexon, pVIII, 33K or 100K would render the product replication-defective. (Ex. 2009 Spindler Decl. at ¶ 58).

32. Nothing in the '512 application teaches the use of helper cell lines which would make it possible for a person of ordinary skill in the art to grow a replication-defective PAV3. (Ex. 2009 Spindler Decl. at ¶ 59).

33. In August 1997, no helper cell lines for growing any replication-defective form of PAV3 were available. (Ex. 2009 Spindler Decl. at ¶ 59).

34. Extensive experimentation is required to produce a new helper cell line. (Ex. 2009 Spindler Decl. at ¶ 59 (*citing* Ex. 2016, Horwitz, at page 2166)).

35. The teachings of the '512 Application do not clearly convey that Johnson had possession of any recombinant PAV3 incorporating foreign DNA into map units 50-55, 55-65, 72-85. (Ex. 2009 Spindler Decl. at ¶ 60).

36. Johnson claims 28 and 71 are directed to a recombinant PAV3 incorporating heterologous DNA in the region identified as encompassing map units 97 to 99.5 (Ex. 2009 Spindler Decl. at ¶ 61 (*citing* Ex. 2002)).

37. The '512 application teaches that map units 97-99.5 encompass "[n]on-essential regions of the viral genome which may be suitable for the purposes of replacement with or insertion of heterologous nucleotide sequences." (Ex. 2009 Spindler Decl. at ¶ 61).

38. The '512 application discloses a non-essential region where insertions can be made as "regions at the right terminal end of the genome at map units 97-99.5." (Ex. 2009 Spindler Decl. at ¶ 62 (*citing* Ex. 2002, at page 5, line 18-20)).

39. The '512 application purports to further specify the area for insertion in Figure 4, which allegedly identifies the putative TATA site for the E4 promoter, "this being the left most end for the possible site of insertion." (Ex. 2009 Spindler Decl. at ¶ 62 (*citing* Ex. 2002 at page 11, lines 29-30)).

40. A TATA site is a sequence of nucleotides that is essential for the expression of the genes that are associated with it. (Ex. 2009 Spindler Decl. at ¶ 62).

41. E4 plays major roles in late gene expression and regulation of transcription. (Ex. 2009 Spindler Decl. at ¶ 63 (*citing* (Ex. 2025 Reddy (1997) at page 87)).

42. Because E4 is an essential region, an insertion downstream of the TATA site could disrupt E4 expression and destroy the PAV3 vector's ability to replicate. (Ex. 2009 Spindler Decl. at ¶ 63).

43. Figure 4 of the AU application identifies the referenced TATA site in bold type at nucleotides 698-701. (Ex. 2009 Spindler Decl. at ¶ 64 (*citing* Ex. 2003)).

44. The map unit range of 97 to 99.5 approximates the area between the bolded ITR (nucleotides 1-144) and the bolded TATA site in Figure 4. (Ex. 2009 Spindler Decl. at ¶ 64).

45. The TATA site called out in Figure 4 of the AU application, (Ex. 2003) however, is not the TATA site for E4 transcription. (Ex. 2009 Spindler Decl. at ¶ 65 (*citing* Ex. 2025, Reddy (1997) at page 88, Figure 1)).

46. Ex. 2025 (Reddy et al.) showed a physical map of the PAV3 genome of a 3028 nucleotide fragment encompassing the right end of the genome as Figure 1. (Ex. 2009 Spindler Decl. at ¶ 65).

47. In Figure 1, Reddy identified features including the locations of the right hand ITR, the E4 region, the polyA signal and two TATA sites corresponding to putative transcription initiation sites. (Ex. 2009 Spindler Decl. at ¶ 65 (*citing* Ex. 2025 Reddy (1997), at page 88, at Figure 1)).

48. Pages 88-89 of the Reddy paper report the results of experiments to determine the 5'-end of the E4 transcripts. (Ex. 2025; Ex. 2009 Spindler Decl. at ¶ 66)

49. The data in the Reddy paper indicate that transcription initiates 22-24 nucleotides downstream from the 3' end of the TATA box between nucleotides 324 and 327. (Ex. 2009 Spindler Decl. at ¶ 66 (*citing* Ex. 2025, Reddy (1997), at pages 88-89)).

50. Thus, the active TATA site for E4 corresponds to nucleotides 324-327 shown in Figure 4 of Johnson's AU application (Ex. 2009 Spindler Decl. at ¶ 66 (*citing* Ex. 2003)).

51. Thus, claims 28 and 71 of the '512 Johnson application encompass within their scope portions of E4 that are essential to viral replication – namely portions of the E4 region genes, including the TATA site of E4. (Ex. 2002; Ex. 2009 Spindler Decl. at ¶ 67).

52. Some of the embodiments of these claims could disable the E4 region genes, rendering the virus helper-dependent. (Ex. 2009 Spindler Decl. at ¶ 67).

53. To practice the full scope of these claims, it would be necessary to provide a helper cell line capable of replacing the function of the disabled E4 genes. (Ex. 2009 Spindler Decl. at ¶ 67).

54. Because the '512 application does not describe a suitable helper cell line or enable a person of skill in the art to produce such a cell line without undue experimentation, the teachings of the '512 Application do not enable one of skill in the art how to make and use a PAV3 vector with insertions within the full range of map units 97-99.5 without undue experimentation. (Ex. 2002; Ex. 2009 Spindler Decl. at ¶ 68).

55. In the priority AU application, no map unit range is disclosed for the E3 region. (Ex. 2003)

56. The '512 Application describes the range of 81-84 as being a "non-coding region" that overlaps with L4. (Ex. 2009 Spindler Decl. at ¶ 69 (*citing* Ex. 2002, at page 5, lines 20-21, and page 11, line 33)).

57. There are no non-coding regions of E3. (Ex. 2009 Spindler Decl. at ¶¶ 69 and 71).

58. E3 does not overlap with L4. (Ex. 2009 Spindler Decl. at ¶ 69).

59. Johnson's original PCT application discloses two PAV genome sizes of 34.8 kb, or 35 kb (Ex. 2004 at page 4 line 20 and Figure 1).

60. The '512 Application suggests inserting foreign DNA into the E3 region after the polyadenylation signal of L4. (Ex. 2009 Spindler Decl. at ¶ 70 (*citing* (Ex. 2002, at page 11, bridging sentence to page 12)).

61. A person of skill in the art might interpret the term "L4" in the '512 Application to refer to L5 of PAV3, since L5 is analogous to the L4 region of the well-known HAV2. (Ex. 2009 Spindler Decl. at ¶ 70).

62. The end of a messenger RNA is formed 10 to 30 nucleotides downstream of the polyadenylation signal which is a specific nucleotide sequence (AAUAAA). Thus, the polyadenylation signal is found 10-30 nucleotides upstream from the end point of the

genes associated with a given region. As a result, genes that share a common polyadenylation signal are co-terminal. In PAV3, E3 and L5 share a common polyadenylation signal. (Ex. 2009 Spindler Decl. at ¶ 49).

63. The '512 Application does not enable a person of skill in the art to insert foreign DNA into a "non-coding region" of E3 after the polyadenylation signal of L5. (Ex. 2002; Ex. 2009 Spindler Decl. at ¶ 72).

64. Using the 34.8 kb PAV3 genome size disclosed in the AU application and the unamended PCT, map unit ranges 81 to 84 correspond to nucleotides 28,188 and 29,232 of PAV3. (Ex. 2009 Spindler Decl. at ¶ 72).

65. E3 encodes for several genes that modulate the response of the host cells to adenovirus infection. (Ex. 2009 Spindler Decl. at ¶ 21 and Ex. 2022, Reddy at p. 98)

66. Encompassed within the range of nucleotides 28,188 to 29,232 is the gene that encodes for fibre. (Ex. 2009 Spindler Decl. at ¶ 72).

67. Fibre is an essential structural element of PAV3. (Ex. 2009 Spindler Decl. at ¶ 72).

68. The splice acceptor site of the fibre gene begins at nucleotide 28910. (Ex. 2009 Spindler Decl. at ¶ 72 (*citing* Ex. 2029 at page 415, Table 2)).

69. Accordingly, some embodiments within the scope of Claim 30 are replication-defective. (Ex. 2009 Spindler Decl. at ¶ 72).

70. Johnson does not describe or enable the production of replication-defective recombinants of PAV3. (Ex. 2009 Spindler Decl. at ¶ 73).

71. A person of skill in the art would not have been able to produce replication-defective recombinants of PAV3 without undue experimentation. (Ex. 2009 Spindler Decl. at ¶ 73).

72. Claim 26 of the '512 Johnson application is directed to a recombinant adenovirus wherein the foreign DNA is "integrated into the non-essential regions of the porcine adenovirus genome." (Ex. 2009 Spindler Decl. at ¶ 74 (*citing* Ex. 2002)).

73. The '512 application does not show which regions of PAV3 are non-essential and which are essential. (Ex. 2009 Spindler Decl. at ¶ 74).

74. In August 1997, it was not known which regions of PAV3 would prove to be essential for viral replication. (Ex. 2009 Spindler Decl. at ¶ 74).

75. The question of which regions of PAV3 will prove to be essential for viral replication is still under active investigation in the art. (Ex. 2009 Spindler Decl. at ¶ 74).

76. It is not possible to predict with confidence which regions of PAV3 are non-essential based on an understanding of other PAV serotypes or of non-porcine adenoviruses, because homology between PAV3 and other PAV serotypes is not sufficient to identify essential PAV3 regions based information that may be available regarding other PAV serotypes. (Ex. 2009 Spindler Decl. at ¶ 74).

77. Without knowledge which regions of PAV3 are non-essential, it is impossible for a person of ordinary skill in the art to practice the full scope of claim 26. (Ex. 2009 Spindler Decl. at ¶ 74).

78. Johnson first added map-unit limitations to his claims in an amendment dated February 27, 2004, in which he purported to limit his claims to the right hand end of the genome "from about 50 genomic map units to 100 genomic map units." (Ex. 2033 at page 2).

79. He argued that support was found in the disclosure of insertions of foreign genes into the "right hand end of the genome." (Ex. 2033 at page 7).

80. The specification makes clear, however, that the term "right hand end of the genome" in Johnson's disclosure refers only to map units 97-99.5, not the entire right half of the genome from map units 50 to 100. (Ex. 2002 at 13, lines 5-8 and 17-21).

81. The art relevant to the technology at issue in this interference is the preparation of animal adenovirus-based vectors for administration to mammals. (Ex. 2009 Spindler Decl. at ¶ 9).

82. A person having ordinary skill in this art in 1996-1999 would have had at least a Master's degree in the biological sciences and/or a Bachelor's degree with at least two years of experience in adenoviruses and have been familiar with scientific and technical publications concerning animal adenoviruses and in particular, porcine adenoviruses. (Ex. 2009 Spindler Decl. at ¶ 9).

83. Using 34,094 bp as the genome size, map units 81 to 84 corresponds to nucleotides 27,616 to 28,639. ((Ex. 2009 Spindler Decl. at ¶ 41)).

84. Using 35 kb as the genome size, map units 81 to 84 corresponds to nucleotides 28,350 to 29,400. ((Ex. 2009 Spindler Decl. at ¶)).

85. In some cases, the genes that are disrupted may be essential to the formation of the adenovirus rendering the resulting vector "replication-defective." (Ex. 2009 Spindler Decl. at ¶ 22)

86. In such cases, the adenovirus recombinant cannot form except in the presence of a "helper" cell that is designed to supply the missing protein or proteins that are associated with the disabled gene or genes. (see Ex. 2016, Marshall S. Horwitz, Ch. 68: Adenoviruses, FIELDS VIROLOGY B. N. Fields B.N. et al. eds. Lippincott – Raven Publishers, Philadelphia, 2149-2171, at 2165-2166 (1996); Ex. 2009 Spindler Decl. at ¶ 22).

87. Human adenoviral vectors with insertions in the essential region E1 are produced in complementing cell lines such as the human embryonic kidney "293" cell line, which expresses E1 proteins. (Ex. 2017 F. L. Graham, et al., Characteristics Of A Human Cell Line Transformed By DNA From Human Adenovirus Type 5, JOURNAL OF GENERAL VIROLOGY 36, 59-72 (1977); see Ex. 2016, Horwitz, supra at 2166, right column; Ex. 2009 Spindler Decl. at ¶ 23)

88. The Reddy patent-in-interference (the '343 patent) discloses "helper-dependent" recombinant adenovirus vectors grown in helper cell lines. (Ex. 2001 the '343 patent, col. 22 line 46 – col. 23, line 16)

89. By experimentation it is sometimes possible to identify certain areas of the adenovirus genome that are not essential to viral replication. (Ex. 2009 Spindler Decl. at ¶ 24)

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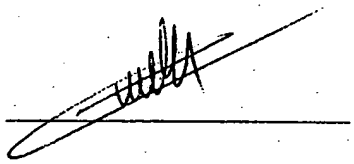
By: 

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